Black cohosh for menopausal Symptoms

Literature Review

Clinically, menopause is diagnosed when previously menstruating women are not menstruating for at least a year or 12 months due to decreased ovarian functions. Menopause is prevalent among women between 45-54 age group (Borrelli and Ernst 2008). Menopause leads to several health consequences and vasomotor symptoms as depressive mood, emotional and psychological distress, hot flashes, cardiovascular effects, skeletal disorders, urogenital complaints, and somatic disorders (Frei-Kleiner, Schaffner et al. 2005).

Hot flashes are the serious and most common symptom of menopause. Hot flashes are the rapid exaggerated feeling of warmth beginning from the chest and going through the neck to the face. The common symptoms of hot flashes are chills, sweating, and flushing (Freedman 2014). During menopause, estrogen withdrawal seems to be the triggering factor for hot flashes (Borrelli and Ernst 2008).

HRT or Hormone Replacement Therapy is the world-known treatment for menopausal symptoms. However, literature shows that the hormone replacement therapy (HRT) taken to relieve symptoms in menopause is linked to the risen chance of developing breast cancer (Vinogradova et al., 2020) together with venous thromboembolism (VTE) (Sweatband et al., 2012), and other diseases such as ovarian cancer (Mørch et al., 2009). Furthermore, the risk is directly correlated to the duration of the treatment (Million Women Study Collaborators; 2003; Vinogradova et al., 2020). Therefore, while on the one hand, HRT is an effective treatment to relieve symptoms of menopause (Taylor & Manson, 2011), on the other hand, it is linked to reduced survival benefit with prolonged usage (Grodstein et al., 1997); however, the risk is lower in women with a lesser chance of developing heart disease (Grodstein et al., 1997).

As a result of overwhelming evidence that HRT may affect women's health by its side effects, the majority of the UK female population does not use HRT in menopause (Cumming et al., 2015). Approximately 80% of women experiencing menopause have symptoms, but only about 10% of them use HRT, especially in some areas of the UK (Newson, 2016). However, emerging evidence shows that the risk of endometrial cancer remains still 2.3 times higher in women using HRT in comparison to non-users (Grady et al., 1995); the risk increases in a linear manner with increased BMI, and it also persists after the treatment is ceased (Grady et al., 1995).

Since the publication of HRT-related side-effects, there is a progressive interest in therapies (non-hormonal) with herbal medicines (Frei-Kleiner, Schaffner et al. 2005). Consequently, there is hope that the menopause symptoms affecting women’s health of the world population could also be enhanced by targeting and promoting certain herbal remedies that may improve vasomotor symptoms of menopause for example, hot flashes and night sweats which represent the most severe symptoms in late perimenopause and post-menopause reaching up to 80% among African Americans (Gold et al., 2006).

Complementary and alternative medicine (CAM) which include herbal therapies are the most common treatments for menopause (Guttuso Jr 2012). Black cohosh or Cimicifuga racemosa (CR) is a promising herbal medicine for menopausal symptoms. Racemosa rhizome tends to include N-methyl cytisine, cimicifugoside, flavonoids, triterpene glycosides, 27deoxyactein, phenolic acids, tannins, and cimicifugin (Farzaneh, Fatehi et al. 2013). Black cohosh has pharmacological effects which may be described as SERM (selective estrogen receptor modulator) augmented by CNS (central nervous system) (Farzaneh, Fatehi et al. 2013). Furthermore, black cohosh has other progestogenic, dopaminergic, and serotonergic effects as well (Shahnazi, Nahaee et al. 2013). Accordingly, more recent scientific evidence to support these recommendations indicates that preparations containing black cohosh play an important role in reducing symptoms of menopause (Kargozar et al., 2017).

The first approach to herb-based medicine occurred approximately from 1620 to 1820 in Europe, North America, and British Isles (Mayo, 1999). With the late modern period, researchers from different countries started to study the curative properties of plants as alternatives to conventional medicine (Mayo, 1999). Responsive theories about the healing properties of such plants continued to be recognized, particularly in relation to women's health, with a focus on menopause (Mayo, 1999).

Black Cohosh, also known by its scientific name as Actaea Racemosa, is a flowering plant originating from North America and deriving from the Buttercup family (Shahnazi et al., 2013). It is rich in phytoestrogens (Shahnazi et al., 2013), compounds found in the plant world, structurally and functionally similar to human estrogen, but not released within the human endocrine system (Shahnazi et al., 2013). Among all-natural remedies used for women's health, black cohosh is the most investigated and popular remedy because of its beneficial effect in strongly reducing menopausal vasomotor symptoms (Shahnazi et al., 2013).

Shams et al. (2010), after reviewing evidence-based literature, reiterated that women with menopausal symptoms showed a 26% decrease in hot flashes and night sweats after taking preparations containing black cohosh (Shams et al., 2010). According to recent findings, black cohosh and primrose oil can be taken as an excellent natural remedy for reducing the hot flashes severity, thus enhancing the quality of life in women going through menopause (Mehrpooya et al., 2018). However, from observations, it appears that black cohosh is much more beneficial and effective in comparison to primrose oil because it reduces not only the intensity of hot flashes, but also the hot flashes number (Mehrpooya et al., 2018). While black cohosh is among those natural remedies most used for alleviating symptoms of menopause (Leach & Moore, 2012), the evidence on its adverse reactions are fragmented and achieved results on its side effects have been shown to be controversial so far (Leach & Moore, 2012). As for example, in the US autoimmune hepatitis was diagnosed in a woman after she used black cohosh to relieve menopause symptoms (Cohen et al., 2004). It was assumed that autoimmune hepatitis was triggered by black cohosh usage (Cohen et al., 2004). A recent investigation reported the association between the black cohosh use and liver damage in about 30 cases in the US (Wobser & 4 of 19Takov, 2020), whereas about 83 cases worldwide of liver damage together with other hepatic disorders were identified in the US and linked to the use of black cohosh too (Wobser & Takov, 2020).

In contrast, another recent study asserted that the cimicifuga racemosa extract (iCR) was well tolerated when administered to women for treating their menopause symptoms (Castelo-Branco et al., 2020) and no side effects were observed compared to placebo (Castelo-Branco et al., 2020). Additionally, evidence of hepatotoxicity was not revealed on that occasion (Castelo-Branco et al., 2020). Besides that, from a small study carried out on women using black cohosh, it was revealed that a 60% of them were less prone in developing breast cancer, concluding that black cohosh may be effective in attenuating breast cancer onset (American Cancer Society, 2020).

The black cohosh plant was chosen as a topic for this systematic review as it has been shown to have a significant positive impact on vasomotor menopausal symptoms' management (De Franciscis et al., 2019).

Menopausal symptoms are challenging, especially in light of the fact that usually most of the symptoms last about 4 years since the last menstrual period occurs (NHS, 2018); however, 1 out of every 10 women faces symptoms for up to 11 years (NHS, 2018). For this reason, it is important to find herbal medicine interventions that effectively facilitate lifestyle changes towards improving quality of life in women experiencing menopausal symptoms

Research Methodology

2 METHODS

The current systematic review is based upon the guidelines provided by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). PRISMA is a 27-items checklist that is incorporated in this systematic review to structure its presentation, development, and framework (Moher et al., 2015).

The current systematic review is conducted through the following steps 1/Formulating the research question and its correspondent target population, 2/Specifying the inclusion criteria, 3/Searching the electronic databases and other available sources, 4/Screening the selected papers, 5/Assessing the risk of bias of the included papers, 6/Reviewing and appraising each paper according to the original research question.

2.1 Data Sources

This systematic review will be conducted by searching all the computerized literature for identifying the interventional or therapeutic studies between 1995 and 2020. All studies will be related to the use of black cohosh supplements for treating menopause vasomotor symptoms. The most common vasomotor symptoms in menopause are night sweats, hot flushes, and further side effects which may have a relation with the utilization of this herb.

Several electronic databases as PubMed, Cochrane Library 2021 (issue 3), BioMed Central, Google Scholar, Embase, Amed, Phytobase, Scopus, and Medline will be searched for finding studies having the primary problem and data on the selected topic. Furthermore, this systematic review will also include unpublished research works as dissertations abstract and British Menopause Society (BMS) reports. Secondary, supplementary research will be based on the bibliographies lists of the selected articles in order to find more studies relevant to the topic research question.

2.2 Search Strategy

The search strategy for this systematic review will be based on the use of specific terms and keywords related to the subjects or topic. The following terms will be used to conduct the literature searching: menopause, vasomotor symptoms, hot flushes, night sweats, climacteric, women's health, black cohosh properties and benefits, black cohosh side effects, herbal remedy, actaea racemosa, phytoestrogens, black cohosh safety, herbal medicines safety, herbal toxicity, and black cohosh hepatotoxicity. The above terms will be combined with boolean search operators such as AND, OR, and NOT (Bramer et al., 2018).

Key words will be used to search for specific concepts (1) efficacy of black cohosh dietary supplements in managing vasomotor menopausal symptoms, (2) Black Cohosh associated with potential adverse effects and/or contraindications, (3) prevalence of HRT to attenuating menopausal symptoms, (4) HRT associated to increased risk of breast cancer development, and (5) most common vasomotor symptoms in women with menopause. Homeopathic preparations won’t be considered for this systematic review. One independent researcher will select articles and assemble them together by screening their abstracts and titles according to the inclusion criteria.

Any studies-related disagreement will be resolved through consultation or consensus by a second and independent reviewer (senior investigator). Full texts will only be retrieved from the research studies which will need to satisfy the elegibility criteria. References lists and citations of the selected papers will also be searched to find additional information about the topic.

2.3 Eligibility Criteria

The eligibility criteria for the selection of studies are evidence-based human interventional research studies as CCTs (Controlled Clinical Trials) and RCTs (Randomized Controlled Trials). All the included articles will be based upon language restriction as English research articles only will be considered. There will be no restriction regarding the number of patients, age group, ethnicity, and type of population.

Eligibility criteria will be including:

Sample (S): Women going through menopause and utilizing the black cohosh supplement therapy for treating vasomotor symptoms of menopause.

Statement of Phenomenon of Interest (SPI): Interventional approaches of interest for this systematic review include, 1) The efficiency of the black cohosh use for relieving the menopause symptoms (vasomotor); 2) Interventions related to adverse effects of the black cohosh use especially looking at liver diseases.

Assessment (A): The primary interest outcome includes any women showing a reduction in menopausal vasomotor symptoms associate with the ingestion of black cohosh supplements. The secondary interest outcome comprises any woman going through menopause and suffering from liver hepatotoxicity potentially linked to the ingestion of black cohosh supplements.

Study Design (SD): All studies will be considered for this systematic review will be based on the intervention strategies correlated to the efficacy of black cohosh in reducing vasomotor symptoms in women with menopause and potential liver-related issue due to the use of this herbal supplement.

Type of Research (TOR): Quantitative data will be applied to drawing up this systematic review.

Supplementary eligibility criteria will be including:

Humans-based interventional studies must (1) evaluate the safety and efficacy of black cohosh supplementations in women affected by menopausal symptoms aiming to therapy, and possible side effects correlated with it; (2) assess the black cohosh’s estrogenic outcome on the risk of the development of liver disease or hepatotoxicity as reported by the occurence of popular live failure cases in women with menopause either having or not having a past personal/family history of liver disorder; (3) Trials will be eligible for this systematic review when conducting on humans and implicating RCTs or CCTs merely; (4) observe the effect (estrogenic) of black cohosh in comparison to the hormone replacement therapy (HRT); (5) assess the black cohosh efficacy for the treatment of night sweats and hot flushes in women with menopausal symptoms.

Due to the lack of data observed in previous studies neither in vivo nor in vitro studies will be used in this systematic review article.

Eligibility criteria will be focused on experimental trials conducted on women in menopause randomly selected from population groups or health care facilities.

In this review will be included interventional studies involving preparations containing black cohosh merged with other natural substances whereas studies involving combinations of chemical substances with black cohosh will not be included in the review. There will be no restriction on the length of the follow-up period carried out in any study.

2.4 Process of Study Selection

One reviewer will search autonomously pertinent information to identify suitable articles for inclusion by reviewing accurately the eligibility criteria labelling articles as ‘eligible’, ‘might be eligible’, or ‘not eligible’ (Van Tulder et al., 2003).

As an intial step of the studies selection process, the screening of the articles according to their titles will be carried out to see if they might be considered relevant to the topic. The second step of this process will involve the reviewer to use abstracts or full texts to assess the eligibility criteria. In the studies selection process, one person only will be involved for the identification of the studies. However, in case of any concernments, the support from a second reviewer or senior investigator will be sought.

2.5 Data Management

The bibliography management will be performed by using the latest version of a specific referencing software/tool named EndNote.

2.6 Data Extraction

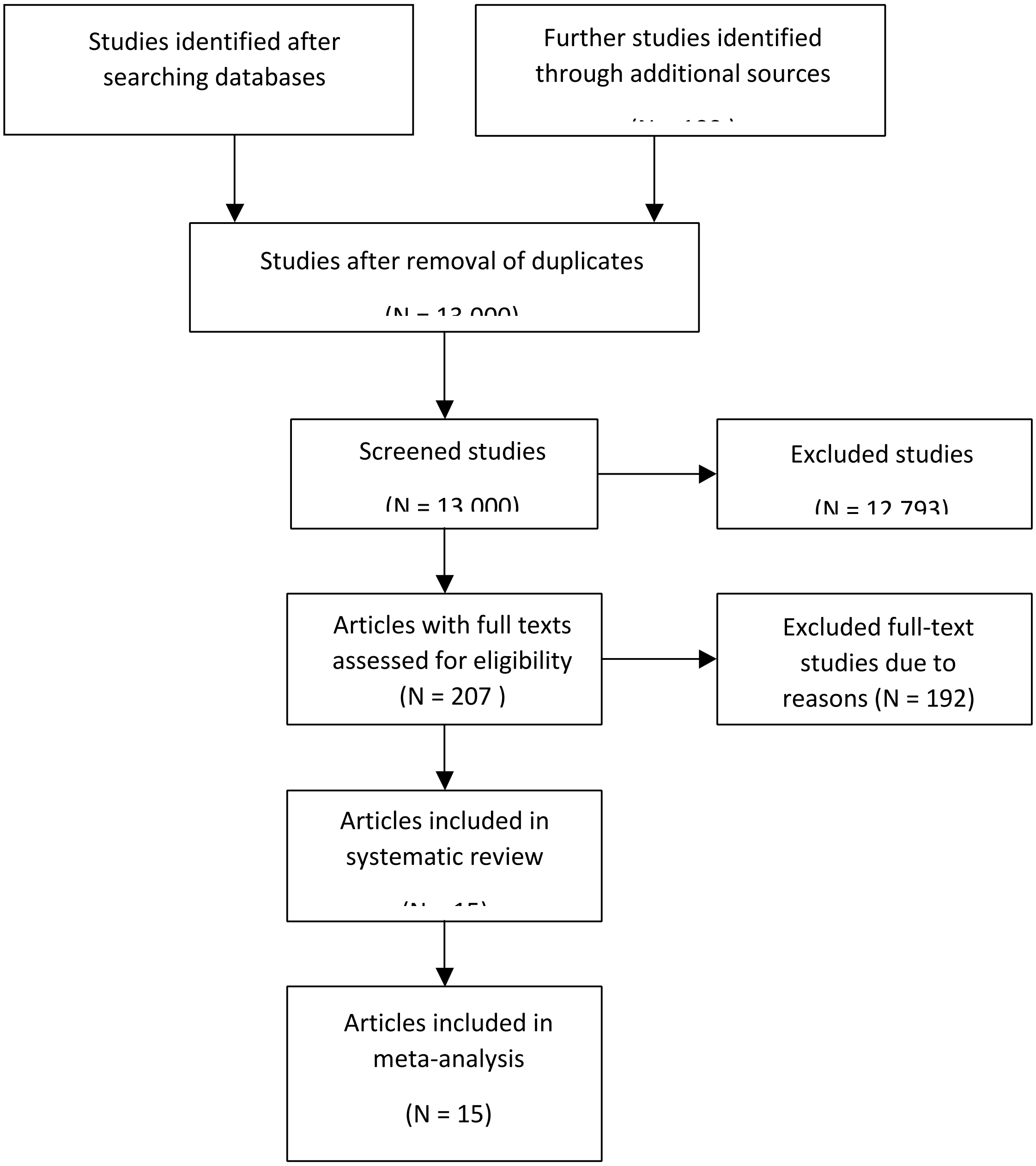
Data will be extrapolated from retrieved articles by one reviewer (LR), and in case of any inconsistency, assistance from a lead researcher will be sought with the purpose of ascertaining clarity and reliability of data. Specific information will be used to extrapolate data. The information are summarised as follows: results/outcomes, size of sample, study design, sample source, intervention/assessment tools, and methods used. Any potential disagreement reconciliation related to the process of the studies selection will be solved through a conversation mediated by a third-person between the two reviewers. In the matter of multiple papers containing similar data, the latest studies only will be contemplated for further processing.

2.8 Risk of Bias Assessment

The National Institutes of Health (NHI) Study Quality Assessment Tools was used to assess the risk of bias in studies evaluating the effectiveness of black cohosh on menopausal vasomotor symptoms and the potential damaging effect it may have on women in menopause (NHI, 2014). As previously stated, one reviewer will assess the risk of bias for each retrieved paper. A special tool called Quality Assessment of Controlled Intervention Studies was implemented in the systematic review to assess data according to the research protocol (NIH, 2014). The Quality Assessment of Controlled Intervention Studies tool consists of fourteen signaling questions that assist the reviewer in determining the risk of bias in each domain.

There are fourteen bias domains in total, and they are sum up as follows: study described as randomised or controlled, intervention allocation, blinding of subjects, similarity of population or sample at the baseline, avoidance of other interventions, assessment of outcome measures, dropout adherence, analysis for intention to treat, power calculation (strengths of study), and pre-specified outcomes. These domains categories were specifically created to help reviewers focus on the most important principles for assessing the study's validity, and hence the study's capacity to draw causal conclusions about the results of the protocol being undertaken.

PRISMA Flow Diagram 2009


Studies identified after searching databases
Further studies identified through additional sources
(N = [illegible])
Studies after removal of duplicates
(N = 13,000)
Screened studies
(N = 13,000)
Excluded studies
(N = 12,793)
Articles with full texts assessed for eligibility (N = 207)
Excluded full-text studies due to reasons (N = 192)
Articles included in systematic review
(N = 15)
Articles included in meta-analysis
(N = 15)

From: Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine, 6*(7), e1000097.

Author	**Study Design**	**Search Engine**	**Outcome measures**
(Wang, C et al., 2019)	RCT	PubMed	Remifemin group and control group (LHRH-a)
(Shahnazi, et al., 2013)	RCT	PubMed	Control group (placebo tablet), Intervention group (Black Cohosh tablet)
(Ross et al., 2012)	Case study	PubMed	Isopropalic black cohosh
(Nasr et al., 2009)	RCT	PubMed	Cimicifuga (40 mg of a dry extract), herbal therapy
(Seo et al., 2021)	Experimental study	PubMed	biomarkers of DNA damage, cell division, and cytotoxicity
(Muqeet et al., 2014)	Case study	PubMed	CT scan and liver biopsy
(Lim et al., 2013)	Case study	PubMed	Liver biopsy
(Huang et al., 2013)	RCT	PubMed	Hamilton depression and Kupperman menopausal indices
(Mehrpooya et al., 2018)	RCT	PubMed	Control group (EPO), Intervention group (black Cohosh), and Menopause-Specific Quality of Life (MENQOL) questionnaire

Table: Characteristics of the studies included in the systematic Review